

Review Article

The Effects of Aging and Electrical Stimulation Exercise on Bone after Spinal Cord Injury

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ABSTRACT: Age related bone loss predisposes adults to osteoporosis. This is especially true for individuals with spinal cord injury (SCI). The effects of decreased bone loading with older age and paralysis significantly contribute to decreased bone mass and increased risk for fragility fractures. Loading bone via volitional muscle contractions or by using electrical stimulation are common methods for helping to prevent and/or decrease bone loss. However the effectiveness and safety of electrical stimulation activities remain unclear. The purpose of this review is to investigate the factors associated with aging and osteoporosis after SCI, the accuracy of bone measurement, the effects of various forms of bone loading activities with a focus on electrical stimulation activities and the safety of physical exercise with a focus on electrical stimulation cycling. Osteoporosis remains a disabling and costly condition for older adults and for those with paralysis. Both dual energy x-ray absorptiometry and peripheral quantitative computed tomography are valuable techniques for measuring bone mineral density (BMD) with the latter having the ability to differentiate trabecular and cortical bone. Physical activities have shown to be beneficial for increasing BMD however, the extent of the benefits related to aging and paralysis remain undetermined. Electrical stimulation activities administered appropriately are assumed safe due to thousands of documented safe FES cycling sessions. However, specific documentation is needed to verify safety and to development formal guidelines for optimal use.

Key words: aging, osteoporosis, spinal cord injury, bone mineral density, electrical stimulation exercise

Over the past century the definition of osteoporosis has changed significantly, from “a reduced amount of bone that is qualitatively normal” [1] to the more current definition: “a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture. Bone strength reflects the integration of two main features: bone density and bone quality”. Bone quality refers to architecture, turnover, damage accumulation (e.g. micro-fractures), and mineralization [2]. In any case, the three main factors that need to be highlighted for an accurate definition of osteoporosis are

1) a decrease in bone mass, 2) a decrease in bone quality and 3) an increased risk of bone fracture.

Typically, bone mineral density (BMD) increases throughout childhood and early adulthood. Bone remodeling becomes the predominant means by which bone is added or removed [3]. From the time of attainment of peak bone mass, late twenties or early thirties, studies show that there is a decrease in bone volume with aging in both sexes [4,5]. Although these changes are not at all sites and not uniform, they mark the start of age related bone loss [5,6].

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The specific cause of these age related changes in individuals is unclear. While it is known that bone mass changes according to the loading history of the individual, there are other factors, such as heredity, nutrition, and co-morbidities that affect bone metabolism [7]. In females, changes in bone are most evident during and after menopause, which is associated with decreased estrogen [7,8]. The decreased estrogen is linked with increased activation of osteoclasts which results in an increased imbalance between resorption and formation causing a more rapid bone loss [5,9]. In males, the reduction in sex-hormone (androgen) production is typically more gradual but also eventually results in a net bone loss as a consequence of increased resorption and decreased formation [10,11]. The prevalence of low bone mass has become a major concern in the United States. According to the National Osteoporosis Foundation an estimated 44 million individuals aged 50 and over are affected by osteoporosis and osteopenia <http://www.nof.org/node/40> which represent 55% of the total U.S. population in that age range. By 2020 the number of individuals 50 and over with osteoporosis or osteopenia in the U.S. is expected to increase to more than 61 million [12]. The World Health Organization has formulated a diagnosis protocol using T-scores to compare the BMD of an individual over the age of 50 with the average BMD of normal bone from able-bodied young adults. The resulting difference is shown as a standard deviation represented as T-scores. T-scores for normal BMD, osteopenia, and osteoporosis are ≥ -1.0 , between -1.0 and -2.5 , and < -2.5 respectively, as defined by the World Health Organization (Table 1). While this score is calculated by measuring the most frequently fractured skeletal areas of able-bodied individuals (lumbar spine, hip, wrist), this location dependent measurement protocol may be less valuable when measuring BMD of those with spinal cord injury (SCI) as the most frequently fractured areas are different (distal femur, proximal tibia) [13-18]. To date there are no standard guidelines concerning the measurement of BMD and the diagnosis of osteoporosis specific to the SCI population.

As reported by the National Osteoporosis Foundation, the cost of osteoporosis in 2005 was approximately 19 billion dollars. This is nearly a 38% increase from the 13.8 billion estimated in 1997. By 2025 the annual cost of osteoporosis is expected to be 25 billion [19]. Additionally, loss of wages, productivity, and other indirect costs are likely to be extensive.

A primary non-pharmacological form of treatment for the prevention and rehabilitation of osteoporosis has been the loading of bone through weight-bearing activities and through exercise with bone receiving beneficial stress via vigorous muscle contractions.

Typically, people become less physically active with age resulting in less mechanical bone loading which is a key factor in stimulating bone formation. Because individuals with complete SCI lack volitional muscle activity below the level of injury, mechanical loading of the bones through electrical stimulation has become a popular modality. However, questions remain concerning the effectiveness and safety of physical activities using electrical stimulation to reduce or reverse the effects of osteoporosis of those with SCI.

The purpose of this literature review is to examine the factors associated with aging and osteoporosis after SCI, discuss the accuracy of BMD measurement, highlight the effects of various forms of bone loading activities with a particular focus on electrical stimulation activities and finally to investigate the safety of electrical stimulation activities with the focus on electrical stimulation cycling.

Table 1. World Health Organization Classifications of Bone

T-score	Classification
≥ -1.0	Normal
$-1.0 - -2.5$	Low bone mass, "osteopenia" (low bone density)
≤ -2.5	Osteoporosis
≤ -2.5 with fragility fracture	Severe osteoporosis

Age related osteoporotic fractures

The primary consequence of osteoporosis is the increased risk of bone fracture. Because age related bone loss is accelerated by menopause, women are twice as likely to experience a fracture as men after age 45 [20,21]. Women over 45 years of age also have a higher likelihood of experiencing an osteoporotic fracture than a traumatic fracture. Osteoporotic fractures, also known as low-trauma fractures or fragility fractures occur with low impact that is consistent with or less than falling from a standing height. This accounts for more than 1.5 million fractures in the U.S. each year and an estimated 9 million worldwide <http://www.nof.org/node/40>.

Effects of spinal cord injury on bone mineral density

Factors that affect the likelihood of osteoporotic symptoms include age, sex, race, diet, physical activity and paralysis [19-23] www.consensus.nih.gov/2000/2000Osteoporosis111html.htm. While a gradual decrease in BMD is a direct effect of aging, SCI is well documented as rapidly accelerating the bone loss process which helps give rise to the term accelerated aging that is

often associated with the SCI population. Within the first few years of complete SCI, individuals experience a rapid 20% -50% decrease in BMD of paralyzed extremities with the exact rate of loss being highly variable among those with SCI [24-36].

In paralyzed individuals, trabecular bone demineralizes more rapidly than cortical bone. This is likely due to the highly metabolic characteristics of trabecular bone. De Bruin *et al* reported that in the spinal cord injured population, trabecular and cortical bone loss in the tibia was 0.4% to 80% and 1.7% to 32.7% respectively [13]. Cortical bone, unlike trabecular bone, demineralizes more gradually due to its less metabolic nature and is characterized by thinning of the cortical wall.

This site-specific bone loss is similar in the upper extremities of individuals with tetraplegia. Here trabecular bone loss was reported to be 19% in the radius as opposed to only 4% loss in cortical bone one year post-injury [14,37]. Furthermore, Saltzstein *et al.* determined a positive correlation between BMD and degree of mobility in the spinal cord injured population [38].

Many studies have looked at the correlation between SCI and fractures occurring after SCI. These studies estimate 5% to 34% of individuals will experience a fracture within the first 5 years after SCI [33,35,39,40] and as many as 70% of all individuals with SCI will sustain a low impact fracture at some point [35]. While there is rapid loss of bone within the first few years post SCI the mean time from injury to the first bone fracture has been reported to be 9 years [15,41].

Because of decreased BMD, individuals with SCI are more likely to experience a fragility fracture than other types of fractures [42,43]. In fact, persons with SCI have a twofold greater risk of fracture than able-bodied individuals with the trabecular rich areas of the distal femur and proximal tibia being most at risk [13-18]. Although there is an acceleration of bone loss below the level of injury, the rate of decrease in BMD varies by bone location [14,31,36]. While the lower extremities experience large decreases in BMD at the distal femur and proximal and distal tibia, changes in the lumbar spine are mixed with reports of both decreases and increases in BMD [13,44,45].

Reflecting the high incidence of fragility fractures, studies show that a large majority of the fractures to the distal femur and proximal tibia after SCI result from falls from wheelchairs or during other low impact activities [42,46,48]. Fracture thresholds have been reported to describe BMD levels at which no fractures have been reported in an effort to provide documentation of safe BMD levels. Eser *et al* determined an approximate threshold of 70mg/cm³ and 110mg/cm³ in the distal tibia

and distal femur respectively in a study of 99 individuals with SCI averaging 12 years post injury [49]. However, a review of BMD by Pors-Neilsen *et al* reported that BMD is a poor indicator of future fracture and many individuals with BMD below these thresholds have safely performed and benefited from physical activities including functional electrical stimulation leg cycle ergometry (FES-LCE) [50].

Due to paralysis and limited mobility of individuals with SCI, specific therapies have been studied and implemented in the effort to slow, and possibly reverse the process of bone demineralization. In order to quantify the effects of SCI and therapies, the measurement of resultant changes in bone mass is required. To date, there is no documented standard of care for the prevention of osteoporotic fractures in individuals with SCI [46,51].

Bone measurement

The key to diagnosis and assessment of systematic bone diseases and disorders is bone densitometry [12,52]. Densitometric studies assess signs of bone instability based on established diagnosis guidelines. The most fundamental parameters in bone densitometry are bone mineral content (BMC), and BMD. BMC is defined as the mass of mineral of bone per unit length of bone (g/cm). BMC however is not as widely used as BMD due to its size-dependent parameters that have been shown to misinterpret and thus misdiagnose individuals of differing heights [53,54].

BMD is a well-known predictor of future bone fracture [23,55-57]. Dual energy x-ray absorptiometry (DXA) is the most commonly used instrument and is considered the "Gold Standard" for measuring BMD [49]. While a quantitative assessment of bone can be performed by DXA, peripheral quantitative computed tomography (pQCT) has the added ability to provide separate analysis of trabecular and cortical bone mineral density [49,55,58,59]. This is important because trabecular bone metabolism takes place at a much faster rate than cortical bone thus, when investigating changes in bone mass due to SCI or a treatment protocol, trabecular bone changes are more likely to be seen first. When examining trabecular bone and cortical bone together as per DXA, changes in trabecular bone may be masked by the lack of change in cortical bone. Along with the ability to distinguish trabecular bone from cortical bone, pQCT accurately measures BMD at the distal femur and proximal femur. This is advantageous in the SCI population due the high rate of fracture as well as differentials in bone growth and demineralization at these locations.

The importance of sensitive bone measurement

Many measurement techniques i.e. (DXA, pQCT, MRI, ultra-sound) are available to assess bone mineral at multiple sites. The most widely validated technique is dual energy X-ray absorptiometry (DXA) scanning of the spine, hip and forearm, <http://www.who.int/chp/topics/Osteoporosis.pdf>.

An important aspect of the use of bone mineral testing in diagnosis of osteoporosis is its relation to fracture prediction. There are significant differences in the performance of different techniques to predict fractures at different skeletal sites. DXA provides measurements of BMD and a gradient of risk for fracture. For example there is an overall increase in fracture risk of approximately 1.5/SD decrease in BMD. The highest gradient of risk provided by DXA is the femoral neck at approximately 2.6/SD [60].

The international reference standard for the description of osteoporosis in postmenopausal women and in men aged 50 years or more is a femoral neck BMD of 2.5 SD or more below the young female adult mean, using normative data from Caucasian women aged 20–29 years. Although the reference standard for the description of osteoporosis is BMD at the femoral neck, other central sites (e.g. lumbar spine, total hip and distal forearm) are used for diagnosis in clinical practice. Z-scores can be used to compare age and gender matched BMD measurements [60].

While traditional DXA can provide BMD scores for total body and regions of interest specific to diagnosis of osteoporosis in the able-bodied population (lumbar spine, proximal femur and wrist), this information misses the more important details from the regions of interest for those with SCI i.e. distal femur, proximal tibia and distal tibia [61]. While some laboratories have developed software that allows modification of DXA measurements to estimate BMD of the distal femur and proximal tibia, this practice is limited. A recent study by Eser *et al.* reported that in the lower extremities, volumetric measurement of trabecular BMD of the epiphyses using pQCT provided evidence that measurement of trabecular bone in the tibia can help discriminate between individuals who have had past fractures and those who have not [49]. Having the ability to provide detailed analysis of bone (trabecular and cortical) may prove to be advantageous for assessing future fractures however long term studies concerning pQCT's ability to assess fractures are needed.

As previously mentioned, DXA does not have the ability to differentiate trabecular bone from cortical bone. Moreover, BMD values when determined by DXA have been shown to be dependent on composition and distribution of soft tissue [50,61,62]. This may be sub-

optimal, as studies have shown that body composition changes significantly after SCI [63,64]. Conversely, measurements performed by pQCT not only distinguish trabecular bone from cortical, but also make osteologic judgments with less influence from the surrounding tissue [56].

It also needs to be clearly understood that DXA measurements of BMD are two-dimensional or areal measurements where as pQCT measurements are three-dimensional or volumetric. For this reason bone size can affect the measurement of BMD as two vertebrae may have identical volumetric densities but have different areal densities. For this reason age may affect the results of DXA scans as the size of bones change during the aging process [12].

Modeling, remodeling, and bone loading

Through the natural process of bone modeling, bone adapts its shape and size as a response to stress or bone loading [55]. During bone modeling, mechanical loading alters the movement and arrangement of osteoclast cells and osteoblast cells, which in turn results in thickening of the cortical wall and improvements in trabecular BMD [55,65-67]. Strain, which is the conditional result of bone loading, has been extensively studied and shown to change the architecture of bone as well as stimulate growth in the process of bone healing [68-72]. Bone remodeling is the process of constant bone removal by osteoclasts and the reformation of new bone by osteoblasts. This method of continuous bone renewal occurs throughout life [55,73].

Opposite of bone loading, bone unloading occurs in SCI individuals due to paralysis and sedentarism. During this time the trabecular lattice rapidly deteriorates and is gradually replaced with fatty marrow [74]. Dauty *et al* conducted a study that showed that the extensive immobility of SCI individuals was the most significant factor in the demineralization of bone in the trochanteric area and proposed that verticulation of the body may help slow the process of bone loss [28]. For the past half century bone loading therapies using standing frames and other aided-walking devices have been studied in attempts to attenuate the effects of osteoporosis in the SCI population [75].

Studies have been mixed concerning the effects of passive standing. While some studies show no significant affect in BMD of individuals that participate in passive standing therapies others have demonstrated that passive standing may have a positive affect during the early stages of SCI [26,76,77]. Studies by Goemare *et al* and Alekna *et al*, reported that individuals participating in prolonged passive standing therapies shortly after SCI had a decreased rate of bone loss at the

femoral shaft according to DXA measurements [78,79]. The attenuating effects of passive standing and walking were studied by de Bruin *et al* using pQCT measurement. Similarly, de Bruin reported a reduced rate of BMD loss overall and that trabecular bone in particular could be preserved with early passive standing and walking interventions [80]. New technology has allowed for testing the advantages of body weight supported treadmill training and mechanical orthosis, but have resulted in limited osteogenic benefits [80-83]. However, it should be noted that few studies reporting the effects of vertical loading on BMD in the SCI population, measure BMD using pQCT. One such study discovered significant benefits in the attenuative properties of passive standing and walking [80].

While static loading therapies such as passive standing are recommended to mitigate the damaging effects of extended bed rest, dynamic bone loading therapies have been recognized as more effective for building BMD [84,85]. Studies involving partial or whole body vibration have been conducted in efforts to more accurately represent the musculoskeletal stresses present in normal activities of daily living (ADL) [86-88]. In a study by Rubin *et al*, sheep were exposed to low levels of high-frequency vibrations while standing in place for 20 minutes per day, five days a week for 1 year. A significant increase in the trabecular BMD was reported [85]. Additionally, studies in whole body vibration (WBV) further showed the benefits of dynamic therapies reporting an increase in BMD in the hips of women post-menopause [86-88]. Limited study has been completed concerning body weight supported treadmill training and its effects on bone mass, with no significant support related to prevention of bone loss [89].

Although this literature review focuses on the effects of decreased mechanical loading on bone after SCI, the reader should be aware that there are other components of bone remodeling impacted by SCI including the endocrine system (blunted anabolic activity, blunted catecholamines and decreased Vitamin D), neurological alterations (sensori-neural and sympathetic nervous system blunting) and increased inflammatory processes as demonstrated by elevated serum levels of C-reactive protein (CRP) a sensitive marker for systemic inflammation that is associated with obesity. However, further discussion of these factors move us beyond the scope of this review.

Electrical stimulation exercise

In the field of SCI rehabilitation, electrical stimulation exercise has become a widely researched and practiced therapy [90]. Due to common paralysis of the lower extremities (LE) in both paraplegia and tetraplegia,

several electrical stimulation exercise therapies involving hybrid orthotics, neuromuscular electrical stimulation (NMES) and leg cycle ergometry have become part of the rehabilitation treatment.

While few studies have investigated the osteogenic benefits of hybrid orthotics to date, these studies report minimal to no effect on BMD [91,92]. However, new hybrid orthotic devices are currently under study which provides encouragement for more positive outcomes in the near future. Several studies have examined the effects of NMES knee extension (KE) on BMD [93-95]. Two of these studies tested effects after 3 months of thrice weekly NMES-KE on individuals averaging 4-6 years post-injury and reported a decrease in the rate of loss of tibial trabecular BMD [93,94]. Additionally, a study by Belanger *et al* reported that when individuals with an average of 10 years post-injury performed NMES-KE 5 times per week for 6 months, 28% of lost BMD in the distal femur and proximal tibia was regained [95]. Unlike some other electrical stimulation therapies, NMES-KE often involves resistance against the paralyzed limb. While this limb resistance is added to increase strain on the bone and thus intensify bone loading, the addition of resistance appeared to have little or no impact on bone as Belanger *et al* reported no significant difference in BMD in limbs exercised with added resistance and those exercised without [95].

Other studies have tested the effects of NMES plantar flexion (PF) on BMD [37,96,97]. Two of these studies tested the effects of NMES-PF performed 5 times per week for >2 years on individuals <4 months post-injury [37,96]. Both of these studies reported an attenuated rate of BMD loss. When NMES-PF was performed 5 times per week for approximately 1 year in SCI individuals averaging 9 years post-injury, no significant osteogenic benefits were reported.

These studies suggest that NMES may help attenuate BMD loss early after SCI with therapy sessions 5 times per week. Also, reports suggest that effects on BMD are site-specific. The affect of inclusion of limb resistance and particular guidelines for training are still to be determined.

Functional electrical stimulation leg cycling ergometry (FES-LCE) has been used in the SCI population to improve glucose uptake and protein expression [98] cardiac output [99], body composition [100], oxygen uptake [99] and increase BMD in the LE [92-94,101-103]. Like other electrical stimulation exercises, FES-LCE produces muscle contractions that in turn apply stress to the bone. Studies on the impact of FES-LCE in SCI individuals have reported both significant increases and decreases in BMD. Because of the wide range of variability in participants and measuring techniques, it is difficult to analyze the

efficacy and safety of this type of bone loading in the SCI population.

In an attempt to cut through the variability, studies with similar variables of interest were grouped together for comparison. In the 10 FES-LCE studies analyzed here, the variables grouped together were: mean time post-injury, mean age of participants, intensity and frequency of therapy, duration of therapy, and measurement techniques/device [94,101-109].

Results of various studies show that FES-LCE has an attenuating effect on rapid bone loss early after SCI. Two studies reporting on the effects of FES-LCE therapy in the first 2 months post injury report a decreased rate of loss. Of the studies performed at an average of 3-6 years post-injury only one study reports

benefits. This study by Bloomfield *et al* reported an increase in BMD in participants who exercised at 18 Watts or more [108]. When the studies were conducted at an average 9-13 years post-injury, significant benefits were reported in 4 out of 5 reviewed studies. It appears that FES-LCE may help slow the process of bone loss in early SCI as well as increase BMD long after SCI. These results are concordant with a study by Eser *et al* that found that bone mass as well as total and trabecular BMD in the femur and the tibia can take 3-8 years to reach a steady state [15]. Studies reporting increases in BMD in individuals averaging 9-13 years post injury indicate that osteogenic effects may be more easily seen after plateauing takes place (Table 2).

Table 2. Effects of Time Post-Injury on FES-LCE Results

< 2 Months	3-6 Years	9-13 Years
<u>Lai <i>et al</i> [104]</u> Decrease in rate of BMD loss in DF (DXA)	<u>Sloan <i>et al</i> [106]</u> No significant difference (DXA)	<u>Chen <i>et al</i> [102]</u> 11% and 13% increases in DF and PT BMD respectively (DXA)
<u>Eser <i>et al</i> [105]</u> Small decrease in rate of BMD loss (pQCT)	<u>Leeds <i>et al</i> [107]</u> No significant difference (DXA)	<u>BeDell <i>et al</i> [109]</u> No significant difference in hip BMD (DXA)
	<u>Bloomfield <i>et al</i> [108]</u> No significant difference in BMD (DXA)	<u>Frotzler <i>et al</i> [103]</u> 14% and 7% increases in DF BMDtrab and BMDtot respectively (pQCT)
		<u>Hangartner <i>et al</i> [94]</u> Decreased rate of BMD loss (pQCT)
		<u>Mohr <i>et al</i> [101]</u> 10% increase in BMD in PT (pQCT)

DF=distal femur; PT=proximal tibia; trab= trabecular; tot=total

In order from least to greatest frequency of therapy (sessions/week) results show osteogenic benefits of FES-LCE may be positively correlated with frequency of FES-LCE therapy sessions. Studies involving FES-LCE therapy 2 times per week showed no benefits while sessions performed 3 times per week were mixed. Notably, only studies consisting of FES-LCE therapy sessions 5 times per week consistently reported substantial improvements in BMD, particularly in the distal femur (Table 3).

Due to the slower bone metabolic processes relative to muscle and fat, it is widely accepted that interventions hoping to produce a measureable change in bone must take place over several months. These studies reflect that belief as all of the studies included interventions of 6 months or greater. Of the FES-LCE studies shown here, there appears to be no direct correlation between the duration of therapeutic intervention and efficacy. However it should be noted that both of the studies that

provided FES-LCE for a minimum of 12 months showed increases in BMD. Significant benefits were also found in the study by Chen *et al* that only had a 6 month intervention period 5 times per week [102]. While there appears to be no direct correlation between duration of FES-LCE therapies after 6 months and BMD benefits, increases in BMD were found in therapies that last at least 6 months (Table 3).

Concerning bone measurement after FES-LCE, Chen *et al* found 11% and 13% increases in BMD at the distal femur and proximal tibia respectively and Lai *et al* found a decrease in the rate of bone loss in the distal femur both using DXA to measure BMD [102-104]. The remaining 4 studies using DXA found no improvements in BMD. This is in contrast to all 4 studies using pQCT which found either increases in BMD or decreases in the rate of bone loss compared to controls. Thus, while not all studies that reported improvements in bone used

pQCT, all of the studies that did use pQCT showed some improvement after training with FES-LCE (Table 3).

Tables 2 & 3 show several notable trends. Studies showed that during periods of rapid bone loss in the early stages after SCI, increases in bone mass were absent although the rate of bone loss was decreased in several studies. However, several years post SCI and presumably after the rate of bone loss had slowed to near age related bone loss, increases in BMD after FES-LCE was possible. Additionally, FES-LCE therapy regimens with higher frequency and duration resulted in greater improvements. Finally, the amount of therapeutic benefit reported from FES-LCE appears to be positively correlated with the ability to examine bone microarchitecture thus it appears that being able to analyze trabecular and cortical bone separately provides valuable information concerning bone alterations with training.

Effects of reduced training and detraining on FES-LCE efficacy

Of the FES-LCE studies examined, 4 incorporated follow up testing concerning the effects of detraining or reduced training on FES-LCE [100-103]. In those that tested detraining, Chen *et al* and Lai *et al* reported that

the rate of BMD loss resumed to pre-training levels after cessation of FES-LCE at 6 months and 3 months respectively [102,104]. However, in a follow up study by Frotzler *et al* where FES-LCE was discontinued after 1 year of cycling 5 times per week, trabecular BMD and total BMD were preserved by 73% and 64% respectively at the distal femur after 6 months [110].

Of the studies testing the effects of reduced training, Mohr *et al* reduced FES-LCE regimen from 3 sessions per week to 1 session per week for 6 months and found that BMD returned to pre-training levels [101]. However, when the FES-LCE sessions were reduced from 5 times per week to 2-3 times per week for 6 months, Frotzler *et al* found that gained BMD was preserved at 95% trabecular BMD and 96% total BMD in the distal femur [110]. While these studies report mixed results, it may be interesting to note that the only study utilizing a measuring device able to examine bone microarchitecture reported preservation of bone with bone reduced training and detraining. In addition to NMES-KE, NMES-PF, and FES-LCE, new technology has allowed the testing of FES rowing therapies. While FES rowing has shown to be beneficial to peak oxygen consumption and peak heart rate in SCI individuals, no found studies report benefits to bone [111,112].

Table 3. Effects of Frequency and Intensity on FES Therapy Results

2 sessions/week	3 sessions/week	5 sessions/week
BeDell <i>et al</i> [109] No significant difference in hip BMD (~9 months)	Lai <i>et al</i> [104] Decrease rate of BMD loss in DF (3 months)	Chen <i>et al</i> [102] 11% and 13% increases in DF and PT BMD respectively (6 months)
Bloomfield <i>et al</i> [108] No significant difference in BMD (~9 months)	Eser <i>et al</i> [105] Small decrease in rate of BMD loss (6 months)	Frotzler <i>et al</i> [103] 14% and 7% increases in DF BMDtrab and BMDtot respectively (12 months)
	Leeds <i>et al</i> [107] No significant difference in BMD (6 months)	
	Sloan <i>et al</i> [106] No significant difference in BMD (3 months)	
	Mohr <i>et al</i> [101] 10% increase in BMD in PT (12 months)	
	Hangartner <i>et al</i> [94] Decreased rate of BMD loss (3 months)	

DF=distal femur; PT=proximal tibia; trab= trabecular; tot=total

Functional electrical stimulation cycling for older adults

There is a lack of research concerning the effects of electrical stimulation activities on older adults as most studies have focused on younger adults. However, in two published case reports of thrice weekly FES-LCE on older adults with chronic SCI, physiological and psychological benefits were shown (increased lean mass, decreased % body fat, and increased scores on quality of life questionnaires) but there were no changes in BMD [113,114]. It must be noted that one study duration was only 8 weeks which is typically considered too soon to see changes in BMD and both studies measured total BMD via DXA which does not have the ability to separate trabecular and cortical bone values. Long term studies using pQCT to measure BMD in older adults with chronic SCI are needed to determine the effects of longer term FES-LCE. In addition the lack of data concerning electrical stimulation activities on older adults with SCI and osteoporosis gives rise to the question of the safety.

Safety: functional electrical stimulation

Safety has become an increased consideration in FES-LCE therapies. This concern was sparked by a study performed in 1984 during which a SCI patient experienced a lateral femoral condyle fracture during the measuring of maximal isometric muscle testing [115]. Even though isometric maximal muscle strength testing is vastly different than FES-LCE, the fact that they both use electricity as the external stimulus creates the need for a closer examination. One major factor that the investigators theorized contributed to the fracture was a spontaneous spasm that took place in the quadriceps and the hip flexors just before the fracture occurred. A review of this case was conducted by Hartkopp and colleagues in which the circumstances surrounding the case were analyzed and further discussed [116].

The subject who experienced the fracture was a 50 year old male 4 years post motor complete SCI at level T6. Within the year before the fracture the subject safely trained using FES-LCE for 6 months (twice a week for 30 minutes per day) in addition to beginning recreational walking therapy. Furthermore, a short time before the study resulting in the fracture, the subject had participated in a tibialis anterior training study lasting for 2 months. The subject also owned a standing frame which he used at home a minimum of 1 hour several times per week. Preliminary measurements found the subject had a BMD that was 40% lower than corresponding age- and sex- matched individuals in the able-bodied population.

After reviewing the case, Hartkopp, *et al* proposed several key experimental factors that they report likely placed extraneous stress on the bone [116]. One major conditional factor that may have precipitated the fracture was the fixed 90 degree flexion of the knee. At this angle, a maximal isometric contraction can have a contact force at the patellofemoral joint of up to 3.4 times the individual's body weight [117]. Studies suggest that testing with the knee flexed approximately 30 degrees can reduce this compression force at the patellofemoral joint by 40% [117,118]. The dangers of ES on a fixed limb are non-existent in FES-LCE as FES-LCE limbs are constantly moving and never fixed. Additionally, in the case of the fracture, electrical intensities were reported to be up to 800 mA and the intensity together with the muscle spasm was estimated to produce a force of 92.5 Nm on the fixed limb. This extreme intensity is far above conditions in FES-LCE that typically have a maximum electrical current of 140mA. This removes any unnecessary stress on the limb during exercise.

Another safety recommendation proposed by Hartkopp *et al* was to reduce electrical stimulation frequency to 50 Hz or less to reduce the likelihood of spasm. This recommendation is well respected in FES-LCE as exercise default settings for electrical frequency are typically 33 Hz [116]. Furthermore, modern FES-LCE equipment such as the RT300 cycle has spasm control features that immediately stop the activity when a spasm is detected. FES-LCE cycles also have safety accommodations that account for resistance speed. These features automatically reduce the amount of resistance if cycle speed drops below a pre-set control speed. This is a safety precaution preventing excessive fatigue.

Lastly, the strength of the bone in relation to the improved strength in LE muscle during FES-LCE was a considered possible safety risk. As has been well established, FES-LCE stimulates improvements in strength in the lower extremities [66,68,95]. This being the case, the fragility of the bone should be taken into consideration. In 2008 Frotzler *et al* published a study establishing similar BMD safety thresholds (114mg/cm³ and 72mg/cm³ for the distal femur and distal tibia). However after muscle conditioning and 12 months of FEC-LCE, participants who initially had BMD below this threshold were above it after the FEC-LCE therapy [103]. Comparable studies using FES-LCE have also reported results showing an increase in BMD at the distal femur and proximal tibia [101-104,108].

The argument can be made that some FES-LCE studies have reported a decrease in BMD [85,95,96]. This being the case, it is also well known that the rate of bone loss in the first couple years of SCI is rapid [13,26,32-36]. Studies that resulted in a decrease in

BMD were conducted within this initial 2 year period. Each also reported a significant attenuation in the rate of loss compared to individuals not receiving FES-LCE therapies. We could find no cases that report an acceleration of bone loss during FES-LCE training.

We were unable to find consistent documentation in most studies concerning the BMD T-scores of participants in order to document the safety records of those with -2.5 or less T-scores (osteoporosis) while participating in FES-LCE. This information is needed to confirm the safety of FES-LCE activities for individuals with chronic SCI and significant bone loss. The absence of reported bone fractures in the literature during FES-LCE, an activity that has been utilized for several decades, indicates the probable lack of bone fractures during this activity and a level of low risk of fracture is assumed. However, documented data is needed for verification.

Concerning the development of osteoporosis after SCI and the effects of physical activity on the development of osteoporosis, in a poster presentation at the "International Society for Clinical Densitometry" in 2009, Sadowski et al reported on the *Prevalence and Risk Factors for Osteoporosis in Individuals with Paralysis*. BMD was determined by DXA of the lumbar spine and bilateral hips. Thirty-three percent (51/154) of individuals with paralysis were found to have osteoporosis, defined as one or more regions with a T-score equal to or less than -2.5. There was no significant difference in the prevalence of osteoporosis with regards to gender (male 33.3 %, female 32.7 %) ($p = 0.94$), or level of injury (tetraplegia 34.8 %, paraplegia 30.8 %) ($p = 0.60$). Osteoporosis was more prevalent in individuals whose injury was over 1 year old (under 1 year injury, 13.3 %, 1-5 years 41.4 %, over 5 years 33.3 %) ($p = 0.024$) [119]. A later poster presentation with the same title presented by Whiting et al at the Kennedy Krieger Institute Research Symposium: Contemporary Trends in Spinal Cord Injury Management, 2012 reported on a total of 290 adults with paralysis using DXA of the lumbar spine and bilateral hips and similarly found that 105 or 36% of the participants had T-scores of -2.5 or less. Using multivariate logistic regression analysis, the researchers estimated that osteoporosis was 61% fewer among SCI participants that were ambulatory and 48% fewer for those that participated in FES-LCE 2 or more times per week [120].

Conclusion

Osteoporosis remains a disabling and costly condition for older adults and for persons with paralysis. While DXA and pQCT are both valuable forms of measurement concerning BMD, pQCT has the unique

ability to differentiate trabecular and cortical bone which is valuable when determining fracture risk and effectiveness of treatments involving bone mass of those with SCI.

There is ample evidence showing that physical activities that provide adequate stress to bone can play a role in the improvement in BMD. Whether these improvements are enough to prevent or reduce osteoporosis and decrease fractures still remains undetermined. Because of the lack of documentation concerning BMD T-scores and osteoporotic identifiers in most of the studies using FES-LCE, it is not possible to quantify the numbers of persons with SCI and osteoporosis that have safely used FES-LCE.

However, we can confidently state that hundreds of individuals with SCI have performed thousands of FES-LCE sessions and due to the lack of documentation concerning bone fractures resulting from FES-LCE, we can state that FES-LCE has been shown to be a safe activity. However, descriptive research data demonstrating safe use of FES-LCE by older individuals with SCI and osteoporosis is needed to verify the assumption that this activity is safe for older adults with SCI and osteoporosis. This data is also needed to provide information for the development of guidelines for optimal and safe exercise parameters.

Declaration of Interest

The authors of this paper have no conflict of interest to declare financially, personally or otherwise.

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